and secretion of an elastase inhibitor following an insult (excessive UV light) makes sense. Chronic exposure to UV light would cause sustained production of elafin, and the action of transglutaminases will result in an irreversible covalent binding with elastic fibers.

> Teleologically speaking, our skin has ample reason to protect its elastic fibers.

Although this would position the protease inhibitor in exactly the right place to do its job, it also comes with a cost: modification of glutamines and lysines in the elastic fiber constituents. Accumulation of these modifications could in the end severely compromise the biochemical and cell-biological properties of these elastic fibers, including resistance to breakdown and normal turnover, propensity to aggregate, and activation of fibroblasts to increase tropoelastin synthesis. The assertion by Muto *et al.* (2007) that fiber-associated elafin protects against breakdown does not, in itself, explain why there is a strong increase of elastic fiber material in photodamaged skin. There are, however, some lessons to be learned from a mouse model. Chronic UV irradiation of hairless mice is a model for actinic elastosis (Starcher and Conrad, 1995). It was shown, however, that mice that lack neutrophil elastase do not accumulate elastic fibers; this suggests a role for elastase not only in breakdown but also in increased production of elastic fibers. There is no mouse ortholog for the human elafin gene, but mice do have SLPI, which probably has the same function. Taken together, these observations suggest that elastase activity promotes elastin synthesis, possibly in an indirect way following the release of breakdown products of the elastic fibers. This process could be controlled to some extent by the local induction of elastase inhibitors such as elafin (Muto *et al.*, 2007) and SLPI (Wingens *et al.*, 1998). When these safeguards fail, excess elastase activity cannot be controlled. Speculatively, elastic fibers altered by transglutaminase-mediated cross-linking and increased elastin production will in the end lead to the elastotic material seen in photodamaged skin.

CONFLICT OF INTEREST

The author states no conflict of interest.

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Opioids and the Skin: "Itchy" Perspectives beyond Analgesia and Abuse

Martin Schmelz[1] and Ralf Paus[2]

Opioids are intimately linked to central pain inhibition and their abuse potential. Thus, peripheral opioid receptors in the skin have been studied initially with a focus on their peripheral analgesic properties. Recent results, however, clearly indicate that opioids play a specific role in skin homeostasis by modulating keratinocyte differentiation, wound healing, and inflammatory responses.

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Traditionally, opioid research is focused on the powerful inhibition of central pain pathways by opioid receptor ligands, an effect that has been clinically exploited for centuries. Like the habitual abuse of exogenous opioids — a matter of much scientific scrutiny and heated political debate — analgesic therapy with exogenous opioids has long been known to be associated with intense generalized pruritus (Twycross *et al.*, 2003; Gutstein and Akil, 2001). And yet, this ancient lead toward the peripheral activities of opioids has

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only relatively recently been followed up. However, even after the detection of peripheral opioid receptors, again, research tended to focus on peripheral analgesic effects of opioids (Stein *et al.*, 2003), whereas investigations on opioid effects beyond analgesia retained their status as rare orchids in a jungle of pain research (for example, Braz *et al.*, 2001).

With the discovery that defined epithelial-cell populations in mammalian skin itself generate endogenous opioids, such as β-endorphin (Slominski *et al.*, 1992), and use them to modulate multiple different functions (for example, control of hair growth and pigmentation (Furkert *et al.*, 1997; Tobin and Kauser, 2005)), and that wound healing and differentiation in mice are also opioid receptor-regulated phenomena (Bigliardi-Qi *et al.*, 2006), one cannot but consider the skin a "habitual opioid user." We are just beginning to understand which stimuli induce epidermal opioid release such as cannabinoid receptor (CB2) activation (Ibrahim *et al.*, 2005) but are still struggling to figure out what our skin is using these opioids for.

Bigliardi-Qi *et al.* (2007, this issue) now open a new perspective on the role of opioid signaling in the epidermis that is unrelated to pain or analgesia, yet relevant to our slowly evolving understanding of the pathogenesis of itch (Paus *et al.*, 2006a; Steinhoff *et al.*, 2006). These authors found that μ- and κ-opioid receptor knockout mice have a markedly thinner epidermis. Moreover, inflammatory changes induced by a combined acetone/ether and water application were reduced in both knockout mice. This supports the notion of an intimate link of opioid signaling in the regulation of inflammatory processes. Topical application of acetone/ether and water not only disrupts the epidermal barrier but also provokes epidermal hypertrophy and scratch behavior (Miyamoto *et al.*, 2002; Nojima *et al.*, 2004) — even though this is not accompanied by a significant influx of inflammatory cells in the treated skin areas (as Bigliardi-Qi *et al.* (2007) confirm).

Examining the interaction of keratinocytes and peripheral nerves histologically, the authors found that the persistent growth of keratinocytes in the epidermis forces the most superficially located C-fibers to constantly extend their endings (Bigliardi-Qi *et al.*, 2007). However, in peripheral sensory neuropathy, epidermal nerve fibers might no longer be able to keep up with the sustained hyperproliferation of keratinocytes and, thus, might end up terminating abruptly at the dermoepidermal junction in diabetes patients (Kennedy *et al.*, 2005). A similar mismatch can result from acetone/ether-induced epidermal hypertrophy, which leaves the intraepidermal nerves "stretched" in appearance and more sparse (Bigliardi-Qi *et al.*, 2006). It is interesting to note that, in both situations, the ratio of keratinocytes to nerves increases, which may result in a higher availability of neurotrophins to the epidermal nerve fibers, thus leading also to sensitization of their endings (Griffin, 2005).

> A new perspective on the role of opioid signaling in the epidermis that is unrelated to pain or analgesia.

Therefore, the current study illuminates a novel aspect of the interaction between keratinocytes and peripheral nerves: whereas earlier work has mainly studied the consequences of impaired nerves for primarily normal epidermal function (Li *et al.*, 1997), Bigliardi-Qi *et al.* (2007) have studied the response of primarily normal epidermal nerve fibers to experimentally induced epidermal hyperproliferation.

This is where the story becomes "itchy." Pruritus can be reduced by painful stimuli, but vice versa, spinally administered μ-opioid agonists can induce segmental analgesia, often combined with segmental pruritus. Conversely, κ-opioid antagonists enhance itch in animal models (Kamei and Nagase, 2001), and the κ-opioid agonist nalbuphine reduces μ-opioid-induced pruritus in humans (Kjellberg and Tramer, 2001), as does a newly developed κ-opioid agonist (Wikstrom *et al.*, 2005).

From these results, one would have expected increased scratch behavior in the κ-opioid receptor-deficient mice and reduced scratching in the μ-deficient. Indeed, the authors found some reduction in scratching behavior in the μ-opioid receptor knockout mice, but a similar trend toward less scratching was also evident in the κ-opioid receptor-knockout mice (Bigliardi-Qi *et al.*, 2007). In contrast, reduced scratching behavior matched the reduced epidermal hypertrophy in response to the acetone/ether stimulus in both opioid receptor knockout strains. Therefore, reduced scratching might well be secondary to the intriguing anti-inflammatory effects seen in the opioid receptor knockout mice, rather than indicating an independent peripheral pruritic effect of opioids.

However, irrespective of whether or not independent, opioid receptor-mediated pruritus-inducing pathways exist, the study by Bigliardi-Qi *et al.* (2007) strongly encourages a more systematic exploration of the evidently important and multifaceted, yet still lamentably underinvestigated, functions of peripheral opioid receptor signaling in skin biology and pathology. The pertinence of such opioid research beyond the analgesia horizon is strikingly illustrated by the recently discovered role of μ- and κ-opioid receptors in neuroprotection and in the neuronal differentiation of stem cells (Kim *et al.*, 2006; Narita *et al.*, 2006). It is further supported by the apparent correlation of the β-endorphin serum level with the clinical severity of a chronic inflammatory, intensely pruritic skin disease such as atopic dermatitis (Lee *et al.*, 2006).

Thus, the time has come to advocate a careful dissection of the role of opioid receptor-mediated signaling in the promotion of inflammation- and itch-perpetuating neuro-endocrine-immune signaling loops in the skin (Paus *et al.*, 2006a; Paus *et al.*, 2006b). Nowhere are the peripheral functions of endogenous opioids and their cognate receptors in general — of which we probably have only scratched the surface — more amenable to analysis and therapeutic manipulation than in skin.

CONFLICT OF INTEREST
The authors state no conflict of interest.

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Clues from Alopecia Areata on the Role of Neuropeptides in the Initiation of Autoimmunity

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A fascinating question regarding the pathogenesis of alopecia areata is the potential linkage with the brain. Siebenharr *et al.* demonstrate that substance P fibers are increased in early lesions, and that substance P treatment induces catagen follicles along with activated CD8$^+$ T cells. Potentially, neuropeptides serve as the initial insult resulting in loss of tolerance and autoimmune disease.

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In this issue of the *Journal of Investigative Dermatology*, Siebenharr *et al.* (2007) present data strongly suggesting a role for substance P in alopecia areata. This is of great interest because it provides a potential link between brain and body with respect to the initiation of autoimmune disease. There is considerable evidence supporting an autoimmune pathogenesis for alopecia areata (Gilhar and Kalish, 2006). Alopecia areata has a statistical association with autoimmune thyroiditis and HLA DQB1*03. Histologically, the condition is marked by an infiltrate of lymphocytes around hair follicles, associated with premature catagen, and conversion of terminal hairs to miniature anagen hairs. The hair follicle demonstrates evidence of immune activation including expression of major histocompatibility complex (MHC) class I and class II molecules as well as ICAM-1 on follicular epithelium, where these molecules are usually poorly expressed or absent. The T-cell infiltrate is characterized by perifollicular CD4$^+$ cells and intrafollicular CD8$^+$ cells as well as a T-helper 1 cytokine profile. Immunologic intervention such as treatment with allergic contact sensitizers can induce hair regrowth, supporting a role of immunology in the pathogenesis.

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